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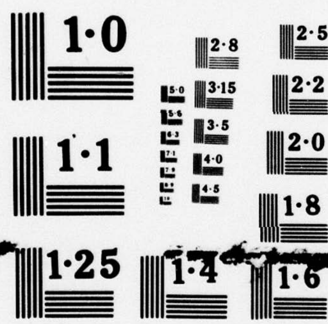

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6 EFFECTS OF METHYLPREDNISOLONE SODIUM SUCCINATE ON CLEARANCE OF LIVE E. COLI FROM THE PERIPHERAL BLOOD OF DOGS.

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in

Circulatory Shock

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Potentiation of infection has been reported as one of the detrimental effects of some corticosteroids (1,2). Recent *in vitro* studies have reported varying degrees of enhancement of bacterial infections, depending on the specific corticosteroid involved (2). Several studies have described the adverse effects of corticosteroids on neutrophil function including depression of chemotaxis (3), depression of mobilization (4), and decreased bactericidal capacity (5,6). Clinical and experimental reports have recently documented the therapeutic effectiveness of methylprednisolone sodium succinate (MP) in the treatment of both septic and endotoxin shock (7,8). Our recent *in vitro* study utilizing baboon blood demonstrated no impairment of *E. coli* mortality in the blood when either high or low concentrations of MP was added to the system (9).

The purpose of this study was to determine if methylprednisolone sodium succinate (MP) affects the clearance of *E. coli* organisms from peripheral blood of dogs.

METHODS

This study was conducted utilizing 12 adult mongrel dogs of random sex. All dogs were selected for freedom of clinical signs of disease, absence of microfilaria of heartworms, treated for intestinal parasites, and stabilized for 3-6 weeks in our animal research facility. Only dogs with peripheral leukocyte counts between 7,000 and 17,000/mm^3 and hematocrits exceeding 35% were utilized in this study.

Both Group A (saline controls) and Group B (methylprednisolone sodium succinate pretreated) were anesthetized with pentobarbital sodium 28-30 mg/kg and allowed 15 minutes for stabilization. Indwelling catheters (Longdwell, Becton, Dickinson & Co., Rutherford, N.J.) were placed in the external jugular vein for obtaining blood samples throughout the experiment. Control blood

samples were then obtained for leukocyte count, hematocrit, blood glucose concentration and bacterial colony count. Blood for leukocyte count, hematocrits and blood glucose concentrations was placed in vacutainers containing ethylendediaminetetraacetic acid (EDTA: Becton, Dickinson & Co., Rutherford, N.J.) and one milliter of blood for colony counts was placed in sterile screw top tubes containing 9 ml of physiological sterile saline (PSS). Both tubes were immediately placed in ice after gentle mixing.

Group B dogs were then given 30 mg/kg of methylprednisolone sodium succinate (MP) intravenously while Group A dogs received equal volumes of saline. Ten minutes after MP and saline administration each dog received live E. coli (mean 3.8×10^9 organisms/kg) intravenously via the cephalic vein. Additional blood samples were obtained at +5 min, +15 min, +1 hr, +2 hrs, +4 hrs, +6 hrs and +24 hrs for leukocyte counts, hematocrits, glucose concentrations and bacterial colony counts. These blood samples were handled as described above.

Total leukocyte counts were measured with an automatic particle counter (Coulter Z_F; Hialeah, Fla.) and the differential WBC by microscopic examination of blood smears stained with Wrights stain (100 cells counted). Blood glucose concentrations were determined with a Beckman glucose analyzer (Beckman Instruments; Fullerton, Calif.) with an accuracy of ± 3 mg%, and rectal temperatures were obtained using a Tele-Thermometer probe (Yellow Springs Instruments, Yellow Springs, Ohio). Blood E. coli concentration was quantitated by serial tenfold dilutions of peripheral blood samples grown in tryptic soy agar pour plates incubated at 37°C for 18-24 hours.

Preparation of the E. coli organisms was as follows: E. coli Type B isolated from a stool specimen at Children's Memorial Hospital, Oklahoma City, Oklahoma, was maintained in a lyophilized state after growth on tryptic soy agar, (TSA). The E. coli was then initially grown in approximately 3-4 ml of tryptic soy broth

at 37°C for 4-6 hours. Tryptic soy agar slants were inoculated from the broth suspension using sterile cotton swabs and incubated at 37°C for 18 hours. The *E. coli* organisms were washed from the slants with 2-3 ml of physiological sterile saline (PSS). The wash was then centrifuged, the supernatant was poured off, and the *E. coli* were resuspended in PSS. The *E. coli* suspension was then adjusted with PSS to a predetermined density using a spectrophotometer (Junior IIA. Coleman Instruments, Oak Brook, Ill). The viability and quanitation of bacterial counts were done using serial tenfold dilutions on TSA pour plates.

The results were analyzed using t tests for paired or unpaired data.

RESULTS

Table I shows changes in bacterial concentrations in peripheral blood after administration of the live *E. coli* organisms. Group A and Group B both significantly reduced ($p<0.05$) the *E. coli* concentration from +15 minutes through +6 hours and +15 minutes through +4 hours, respectively, when compared to +5 minute *E. coli* concentrations. There was no difference ($p>0.05$) in concentrations of live *E. coli* organisms in the peripheral blood between the two groups at any time.

Effects of live *E. coli* organisms on leukocyte concentration in either saline pretreated dogs (Group A) or methylprednisolone sodium succinate (MP) pretreated dogs (Group B) are shown in figures 1A and 1B. After intravenous injection with *E. coli* both groups became leukopenic ($p<0.05$) from +5 minutes through +2 hours. Differential counts reveal that the leukopenia can be accounted for by a decrease ($p\leq0.02$) in mature neutrophils from +5 minutes through +2 hours. Group B dogs had a higher ($p<0.025$) total leukocyte count at +6 hours compared with Group A, but there were no significant differences within or between groups for immature neutrophil, lymphocyte, or monocyte counts.

Blood glucose concentrations are illustrated in figure 2. In the control group (Group A) a hyperglycemia ($p<0.005$) developed at +15 minutes after *E. coli* administration followed by a progressive decrease in blood glucose concentration reaching lower ($p<0.05$) values at +4 and +6 hours. The steroid pretreated group (Group B) exhibited an elevated ($p<0.05$) blood glucose concentration at +5 minutes, +15 minutes and +2 hours after *E. coli* injection; however, Group B developed a lower ($p<0.02$) blood glucose concentration at +4 hours. There were no ($p>0.05$) differences in blood glucose concentrations between Groups A and B from control time through +24 hours.

Changes in hematocrit are shown in figure 3. Both groups' hematocrits increased ($p<0.05$) from +15 minutes through +6 hours when compared with their control values. There were no statistically significant differences between the control and steroid groups.

Figure 4 illustrates variations in rectal temperature for dogs in this study. The steroid group (Group B) had an elevated ($p<0.05$) rectal temperature at +1, +2 and +4 hours compared with the control group. Group B dogs had elevated ($p<0.05$) rectal temperatures at +4 hours when compared with their own control values.

Three of six dogs survived in the MP pretreated group contrasted with one of six saline pretreated dogs. Dogs living a 7-day period following the injection of the live *E. coli* organisms were classified as survivors.

DISCUSSION

Recent reports show enhancement of bacterial infection as one of the detrimental effects of some corticosteroids (1,2). Other adverse effects of corticosteroids include inhibition of chemotaxis (10), depression of mobilization (4), and diminished bacterial capability by neutrophils (2,11,12). Certain corticosteroids in other studies are reported to have no adverse effects on bactericidal

activities of leukocytes (2,13), including engulfment and killing of enteric bacteria (14). A prospective and retrospective study reported by Schumer revealed that both methylprednisolone and dexamethasone decreased the mortality of septic shock in man (7). Our recent study utilizing the canine endotoxin shock model demonstrated a significant increase in survival when treated with MP (8).

Postel and associates using dogs as their experimental model suggested that the host's primary defense mechanism against microbial infections depends primarily on phagocytosis and intracellular killing by neutrophils (15). Stossel has indicated that the neutrophil is the first line of defense against pyogenic infections, while monocytes and macrophages are the second line of defense (16).

A recent *in vitro* study in our laboratory utilizing baboon blood revealed that methylprednisolone sodium succinate (MP) at both therapeutic serum levels and 10 times therapeutic levels produced no change in mortality of live *E. coli* organisms, neutrophil glucose metabolism and neutrophil survival (9). The present investigation was designed as a follow up of the former *in vitro* study and was conducted to establish the *in vivo* effects of MP on bacterial clearance from the peripheral blood, hematocrit, leukocyte and febrile response in the dog.

Findings from the present study demonstrated that there was no difference in clearance of *E. coli* from the peripheral blood between MP pretreated and saline pretreated, and it appears MP did not effect the host defense response in eliminating the live *E. coli*. This is in agreement with earlier *in vitro* studies showing that methylprednisolone does not change neutrophil function (2,9). It is of interest to note the dog's ability to clear by almost two orders of magnitude the number of live *E. coli* organisms from the peripheral blood of both groups when comparing +5 minutes concentration with +2 hour concentration. This *in vivo* rate of clearance of *E. coli* organisms closely parallels the disappearance rate of live *E. coli* from dog blood *in vitro* (17).

The initial leukopenia and subsequent leukocytosis observed in the survivors are in agreement with previous results from our laboratory (18-21). The leukopenia has been shown to be a granulocyte margination and adherence to endothelial cells when phagocytizing bacteria (22-24). Leukocytosis in response to endotoxin has been reported to occur when new leukocytes from the bone marrow enter the peripheral circulation (25). The significantly higher leukocyte numbers at +6 hours in the MP group might be the result of steroid stimulation (26).

The progressive development of hypoglycemia observed in both groups agrees with previous studies using both endotoxin and live organisms (27,28). Groves and associates reported hypoglycemia, depletion of liver glycogen, impaired gluconeogenesis, and lowered serum insulin in the dog subjected to intravenous live E. coli (29). Hypoglycemia has been reported by Rackwitz and associates in septic shock patients (30). The hypoglycemia has also been linked with hypotension, hepatosplanchnic pathology and depressed liver gluconeogenesis (27,28,31).

Rectal temperatures of MP pretreated dogs were significantly higher than the control dogs from +1 through +4 hours post E. coli. This increase in rectal temperature might result from promotion of tissue perfusion, increased blood flow and elevated blood pressure (32,33,35). These findings are in agreement with our previous MP therapy study that revealed both awake and anesthetized dogs receiving endotoxin by either slow infusion or bolus and treated with MP became febrile, while non-steroid treated controls failed to develop increased temperatures (8).

The hematocrit increased significantly in both groups, and animals with the greatest hemoconcentration died. Hemoconcentration has been previously correlated with impending death in dogs subjected to E. coli septic shock (35). Administration of dextran was necessary for maintaining hematocrit constant in awake dogs subjected to E. coli septic shock (27). Survival has been previously associated with a stabilized hematocrit in dogs subjected to endotoxin shock (8).

These data support earlier studies showing that fresh canine blood had a significant capacity to reduce numbers of live _E. coli_ within two hours in the test tube. The present investigation enforces our earlier _in vitro_ study which found that MP did not alter the mortality of live _E. coli_. Results from this study show that methylprednisolone sodium succinate administered intravenously at a therapeutic dose caused no change in the clearance of live _E. coli_ organisms from the peripheral blood of dogs.

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TABLE I. E. COLI CLEARANCE FROM THE PERIPHERAL BLOOD (MEAN $\pm$SE)

E. COLI COLONY FORMING UNITS/ML BLOOD							
TIME	+5 MIN	+15 MIN	+1 HR	+2 HR	+4 HR	+6 HR	+24 HR
GROUP A* SALINE CONTROL	4.0×10^5 ($.8\times10^5$)	5.6×10^4 (1.0×10^4)	1.5×10^4 ($.5\times10^4$)	8.7×10^3 ($.8\times10^3$)	8.6×10^3 (3.0×10^3)	1.1×10^4 ($.6\times10^4$)	1.3×10^3 (1.0×10^3)
P		0.02	0.01	0.01	0.01	0.05	NS
GROUP B* METHYLPREDNISOLONE	5.7×10^5 (2.0×10^5)	4.7×10^4 (1.2×10^4)	1.2×10^4 ($.2\times10^4$)	9.3×10^3 (2.0×10^3)	9.4×10^3 (3.0×10^3)	1.0×10^4 ($.4\times10^4$)	7.5×10^2 (3.0×10^2)
P		0.05	0.05	0.05	0.05	NS	NS
P≠	NS	NS	NS	NS	NS	NS	NS

* = Total of 12 dogs: Group A (N=6) were pretreated 10 minutes before E. coli injection with saline (.6 ml/kg) given intravenously. Group B (N=6) were pretreated with methylprednisolone sodium succinate (30 mg/kg) administered intravenously 10 minutes prior to E. coli. Both groups received E. coli (mean 3.8×10^9 organisms/kg) at 0 time by intravenous injection.

P = Paired comparisons for +15 min, +1, +2, +4, +6, +24 hrs compared to +5 min.

P≠ = Unpaired comparison between Groups A and B.

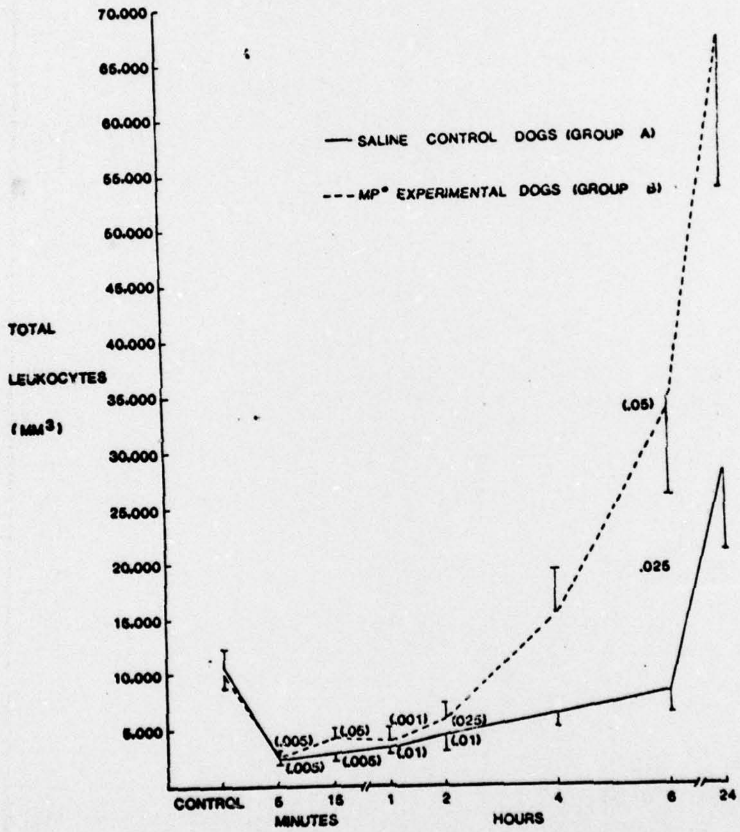
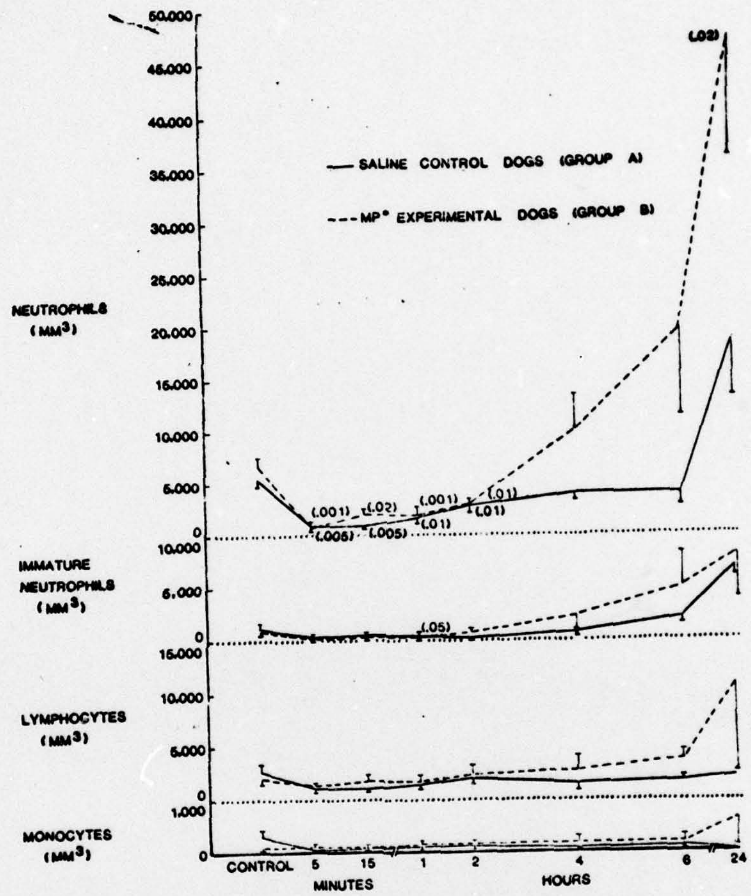

70,000
65,000
60,000
55,000
50,000
45,000
40,000
35,000
30,000
25,000
20,000
15,000
10,000
5,000
TOTAL
LEUKOCYTES
(MM3)
— SALINE CONTROL DOGS (GROUP A)
--- MP* EXPERIMENTAL DOGS (GROUP B)
(.005)
(.05)
(.001)
(.025)
(.005)
(.005)
(.01)
(.01)
(.05)
.025
CONTROL
5
15
1
2
4
6
24
MINUTES
HOURS

Figure 1 A



NEUTROPHILS (MM³)
IMMATURE NEUTROPHILS (MM³)
LYMPHOCYTES (MM³)
MONOCYTES (MM³)
— SALINE CONTROL DOGS (GROUP A)
--- MP* EXPERIMENTAL DOGS (GROUP B)
50,000
45,000
40,000
35,000
30,000
25,000
20,000
15,000
10,000
5,000
0
(.02)
(.001)
(.02)
(.001)
(.01)
(.005)
(.005)
(.01)
(.01)
10,000
5,000
0
(.05)
15,000
10,000
5,000
0
1,000
0
CONTROL
5
15
1
2
4
6
24
MINUTES
HOURS

Figure 1B

Figures 1A & 1B. Total leukocyte and differential leukocyte responses of dogs given intravenous injections of live E. coli (mean 3.8×10^9 organisms/kg) (mean $\pm$SE; N=6 in each group). Both groups were anesthetized with sodium pentobarbital 28-30 mg/kg 25 minutes prior to E. coli injection. Group B dogs were administered 30 mg/kg of methylprednisolone sodium succinate (MP) 10 minutes before E. coli injection. Group A dogs were given .6 ml/kg of saline 10 minutes prior to E. coli administration. P values with no parentheses represent unpaired comparisons between Groups A and B. P values within parentheses are paired comparisons within groups to control time measurements.

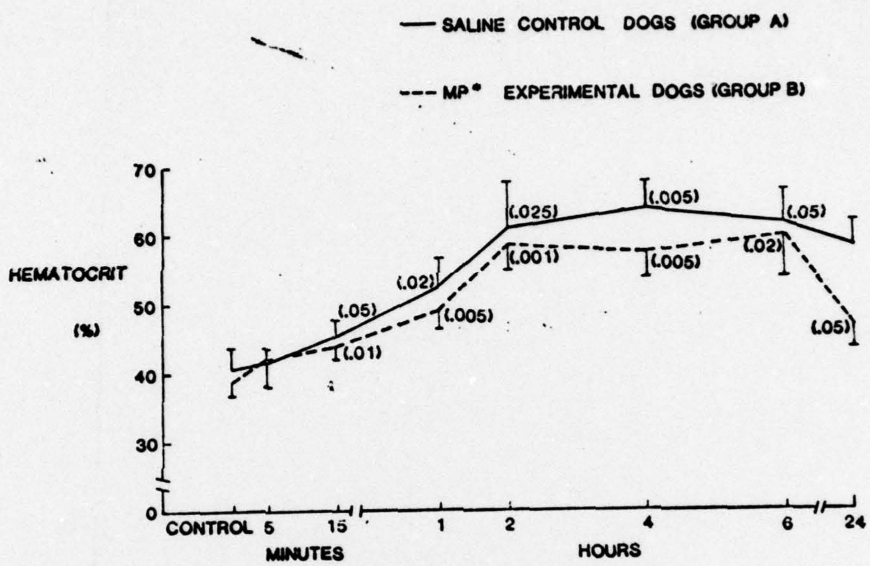


Figure 3. Changes of hematocrit following administration of live E. coli organisms in dogs after pretreatment with either MP or saline (mean +SE; N=6 in each group). (See Figure 1A and 1B for details of experiment).

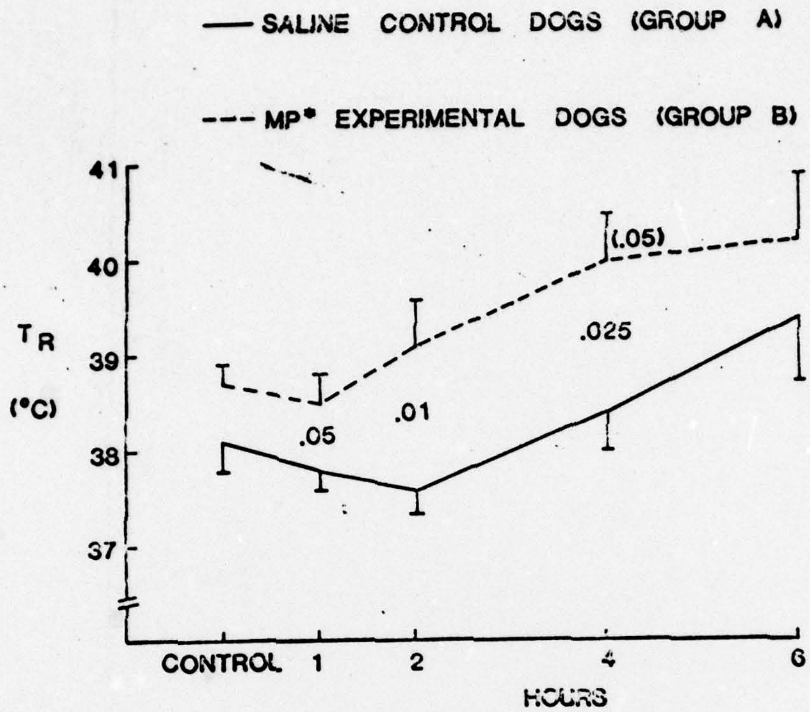


Figure 4. Responses of rectal temperature of dogs injected with live <u>E. coli</u> organisms following pretreatment with either MP or saline (mean ±SE; N=6 in each group). (See Figures 1A and 1B for details of experiment).

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ABSTRACT

Corticosteroids have been reported to potentiate infections, and yet recent clinical and experimental studies have documented their therapeutic effectiveness in both septic and endotoxin shock. This study was designed to determine if methylprednisolone sodium succinate (MP) affects the clearance of live E. coli organisms from peripheral blood of dogs. The experimental group was pretreated with 30 mg/kg of MP while controls received equal volumes of saline. Both control and MP pretreated dogs significantly reduced the number of E. coli in peripheral blood by almost two orders of magnitude; however, there was no significant difference in clearance of E. coli organisms between the two groups. An initial leukopenia occured in both groups after E. coli injections; however, the subsequent development of leukocytosis in the MP group was significantly greater at +6 hours. Rectal temperatures were higher in the MP group from +1 through +4 hours compared with the controls. Hyperglycemia developed initially in both groups followed by a progressive hypoglycemia with survivors returning to near normal blood glucose concentrations. Hemoconcentration occured in both groups with higher hematocrits being associated with mortality. Results support the view that methylprednisolone sodium succinate does not affect the clearance of live E. coli organisms.

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